COMBINATION OF A 3-(IMIDAZOL-4-YL)-4-(AMINO)-BENZENESULFONAMIDE TEAD INHIBITOR WITH AN EGFR INHIBITOR AND/OR MEK INHIBITOR FOR USE IN THE TREATMENT OF LUNG CANCER

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to TEAD inhibitors, compositions thereof, and use of a TEAD inhibitor in combination with an EGFR inhibitor and/or a MEK inhibitor for treatment of cancer.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] This application claims the benefit of and priority to under 35 U.S.C. § 119(e) of United States Provisional Patent Application serial number 63/141,105, filed January 25, 2021; the contents of which are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0003] Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are transcriptional co-activators of the Hippo pathway network and regulate cell proliferation, migration, and apoptosis. Inhibition of the Hippo pathway promotes YAP/TAZ translocation to the nucleus, wherein YAP/TAZ interact with TEAD transcription factors and coactivate the expression of target genes and promote cell proliferation. Hyperactivation of YAP and TAZ and/or mutations in one or more members of the Hippo pathway network have been implicated in numerous cancers.

SUMMARY ~~OF THE INVENTION~~

[0003a] In an aspect of the present disclosure, there is provided a use of a TEAD inhibitor and an EGFR inhibitor in the manufacture of a medicament for treating cancer in a patient in need thereof.

[0003b] In another aspect of the present disclosure, there is provided a use of a TEAD inhibitor and a MEK inhibitor in the manufacture of a medicament for treating cancer in a patient in need thereof.

[0004] It has been found that the combination of a TEAD inhibitor and an EGFR inhibitor has synergistic effects in treating cancer. Accordingly, in one ~~aspect~~example, the present ~~invention~~disclosure provides a method for treating cancer in a patient comprising administering to the patient a therapeutically effective amount of a TEAD inhibitor and an EGFR inhibitor.

[0005] It has been also found that the combination of a TEAD inhibitor and a MEK inhibitor has synergistic effects in treating cancer. Accordingly, in one ~~aspect~~example, the present ~~invention~~disclosure provides a method for treating cancer in a patient comprising administering to the patient a therapeutically effective amount of a TEAD inhibitor and a MEK inhibitor.

[0006] It has also been found that the combination of a TEAD inhibitor and an EGFR inhibitor has additional synergistic effects in treating cancer when used in further combination with an MEK inhibitor. Accordingly, in one ~~aspect~~example, the present ~~invention~~disclosure provides a method for treating cancer in a patient comprising administering to the patient a therapeutically effective amount of a TEAD inhibitor, an EGFR inhibitor, and an MEK inhibitor.

[0007] In some ~~embodiment~~examples, a TEAD inhibitor is selected from those as described herein. In some ~~embodiment~~examples, an EGFR inhibitor is selected from those as described herein. In some ~~embodiment~~examples, an MEK inhibitor is selected from those as described herein. In some ~~embodiment~~examples, a cancer is selected from those as described herein.

BRIEF DESCRIPTION OF FIGURES

[0008] **FIG. 1** demonstrates the apoptosis induction effects of a TEAD inhibitor **T-A-32**, an EGFR inhibitor Osimertinib, an MEK inhibitor Trametinib, and combinations thereof in HCC4006 and HCC827 cells.

[0009] **FIG. 2** demonstrates the effects of a TEAD inhibitor **T-A-32**, an EGFR inhibitor Osimertinib, an MEK inhibitor Trametinib, and combinations thereof on H1975 Tumor Growth in nude nu/nu mice.

[0010] **FIG. 3** demonstrates the effects of a TEAD inhibitor **T-A-32**, a MEK inhibitor Trametinib, and a combination thereof on tumor growth and volume in an HCT-116 tumor model, which is a KRAS G13D mutant tumor.

[0011] **FIG. 4** demonstrates the effects of a TEAD inhibitor **T-A-32**, a MEK inhibitor Trametinib, and a combination thereof on tumor growth and volume in an A549 tumor model, which is a KRAS G12S mutant tumor.

[0012] **FIG. 5** demonstrates the effects of a TEAD inhibitor **T-A-32**, a MEK inhibitor Trametinib, and a combination thereof on tumor growth and volume in a LoVo tumor model, which is a KRAS G12D mutant tumor.

DETAILED DESCRIPTION OF THE INVENTION

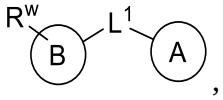
1. General Description of Certain Embodiments of the Invention

[0013] As described herein, a combination of a TEAD inhibitor and an EGFR inhibitor demonstrated unexpected synergistic effects in treating cancer. For example, a combination of a

CLAIMS

1. Use of a TEAD inhibitor and an EGFR inhibitor in the manufacture of a medicament for ~~A method of~~ treating cancer in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a TEAD inhibitor and an EGFR inhibitor~~.

2. The ~~method~~use of claim 1, wherein the TEAD inhibitor is a compound of **Formula A**:



,

or a pharmaceutically acceptable salt thereof, wherein

L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

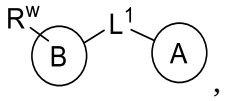
Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^w is an optionally substituted 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each R is independently -H or optionally substituted -C_{1-6} aliphatic. .

3. The ~~method~~use of claim 1, wherein the TEAD inhibitor is a compound of **Formula B**:



,

or a pharmaceutically acceptable salt thereof, wherein

L^1 is a covalent bond, or a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH($N(R)_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

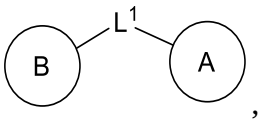
Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^w is a warhead group; wherein when R^w is a saturated or partially unsaturated monocyclic carbocyclic or heterocyclic ring, it optionally forms a spiro bicyclic ring with Ring B; and

each R is independently -H or optionally substituted -C_{1-6} aliphatic.

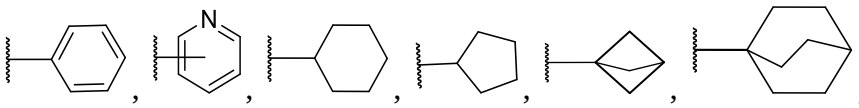
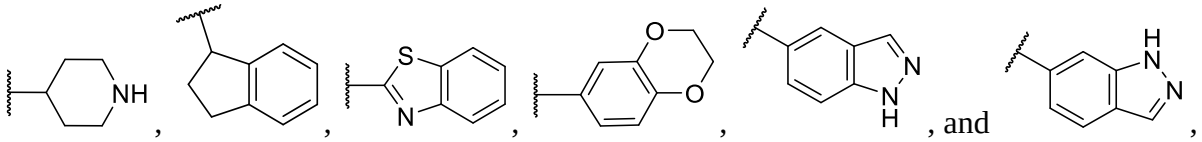
4. The ~~method~~use of claim 1, wherein the TEAD inhibitor is a compound of **Formula C**:

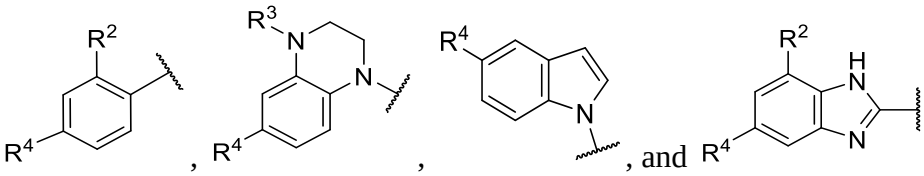


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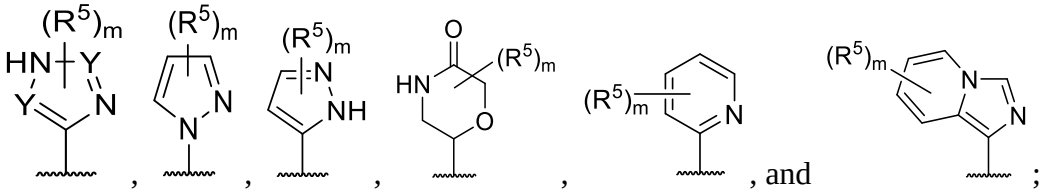
or a pharmaceutically acceptable salt thereof, wherein

L^1 is a covalent bound, or a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

Ring A is selected from , , and , each of which is optionally substituted;

Ring B is selected from , and ;

each R^2 is independently selected from -OR, $-C(O)NR_2$, optionally substituted $-C_{1-6}$ aliphatic,

, and ;

each Y is independently N or CR^5;

R^3 is H, -C(O)R, or optionally substituted $-C_{1-6}$ aliphatic;

each R^4 is independently $-S(O)_2NR_2$, $-S(O)_2R$, $-C(O)NR_2$, -C(O)R, or optionally substituted $-C_{1-6}$ aliphatic;

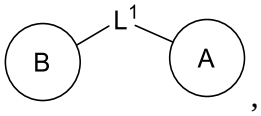
each R^5 is independently R, -CN, -C(O)R, $-C(O)NR_2$, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2; and

each R is independently H, optionally substituted $-C_{1-6}$ aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally

substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

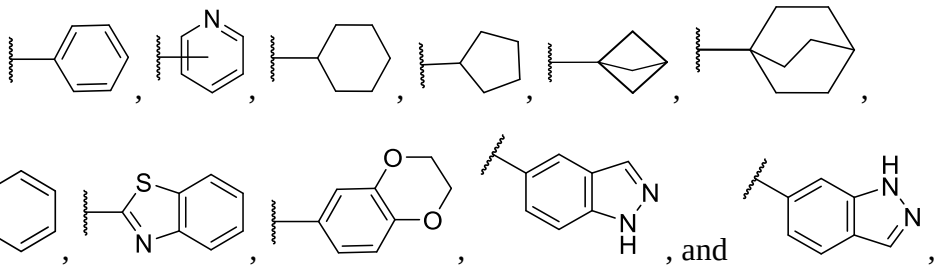
5. The ~~method~~use of claim 1, wherein the TEAD inhibitor is a compound of **Formula D**:



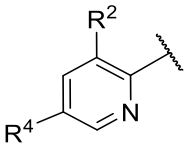
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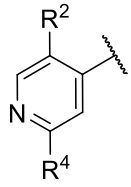
or a pharmaceutically acceptable salt thereof, wherein

L^1 is a covalent bound, or a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

Ring A is selected from 

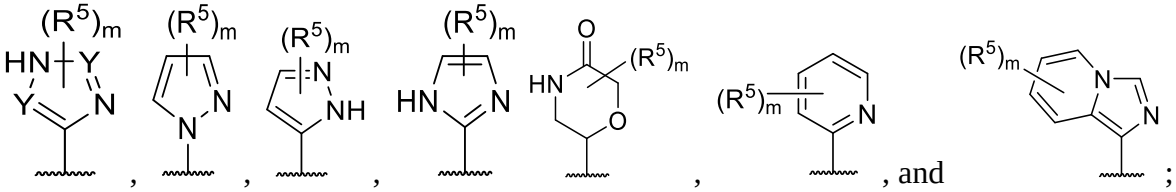
, each of which is optionally substituted;

Ring B is 

or 

;

each R^2 is independently selected from -OR, -C(O)NR_2, optionally substituted -C_{1-6} aliphatic,



;

each Y is independently N or CR^5;

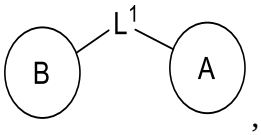
each R^4 is independently -$S(O)_2NR_2$, -$S(O)_2R$, -C(O)NR_2, -C(O)R, or optionally substituted -C_{1-6} aliphatic;

each R^5 is independently R, -CN, -C(O)R, -C(O)NR_2, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2; and

each R is independently H, optionally substituted -C_{1-6} aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

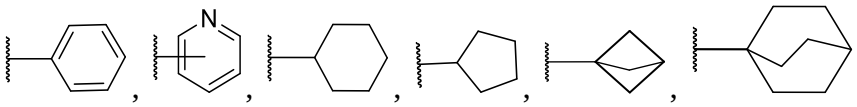
6. The ~~method~~use of claim 1, wherein the TEAD inhibitor is a compound of **Formula E**:

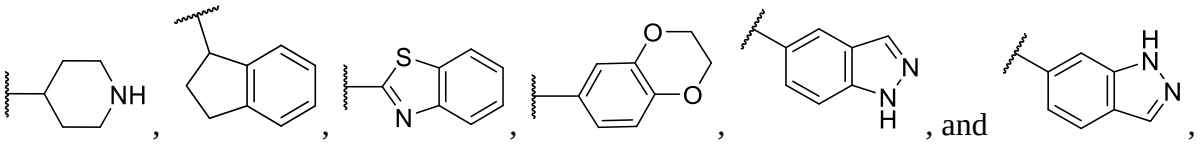


,

or a pharmaceutically acceptable salt thereof, wherein

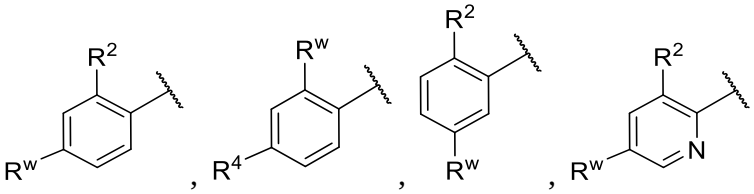
L^1 is a covalent bound, or a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

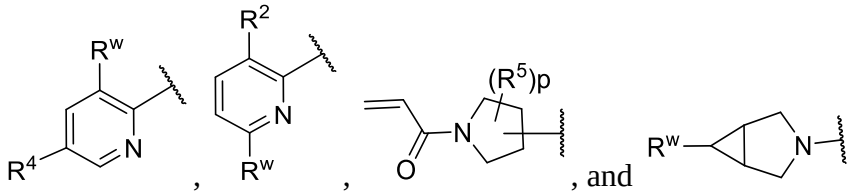
Ring A is selected from 

, 

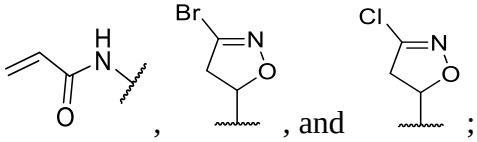
, and
,

each of which is optionally substituted;

Ring B is selected from 

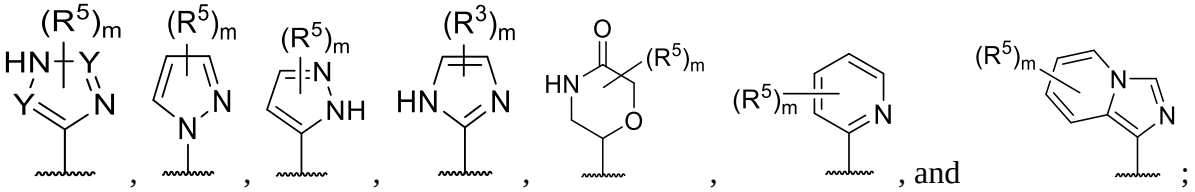
, 

, and ;

each R^w is independently selected from 

, and ;

each R^2 is independently selected from -OR, -C(O)NR_2, optionally substituted -C_{1-6} aliphatic,



, and ;

each Y is independently N or CR^5;

each R^3 is independently H or optionally substituted -C_{1-6} aliphatic;

each R^4 is independently -$S(O)_2NR_2$, -$S(O)_2R$, -C(O)NR_2, -C(O)R, or optionally substituted -C_{1-6} aliphatic;

each R^5 is independently R, -CN, -C(O)R, -C(O)NR_2, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2;

p is 0, 1, or 2, and

each R is independently H, optionally substituted -C_{1-6} aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

7. The ~~method~~use of any one of claims 1-6, wherein the EGFR inhibitor is selected from cetuximab, necitumumab, panitumumab, zalutumumab, nimotuzumab, and matuzumab.

8. The ~~method~~use of any one of claims 1-6, wherein the EGFR inhibitor is selected from osimertinib, gefitinib, erlotinib, lapatinib, neratinib, vandetanib, afatinib, brigatinib, dacomitinib, and icotinib.

9. The ~~method~~use of any one of claims 1-8, wherein the TEAD inhibitor and the EGFR inhibitor are to be administered to the patient, and wherein ~~further comprising administering~~ an MEK inhibitor is to be further administered.

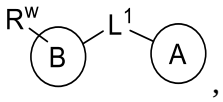
10. The ~~method~~use of claim 9, wherein the MEK inhibitor is selected from refametinib, selumetinib, trametinib, and cobimetinib.

11. The ~~method~~use of any one of claims 1-10, wherein the cancer is an EGFR mutant resistant cancer.

12. The ~~method~~use of claim 11, wherein the cancer is an EGFR mutant resistant lung cancer, or an EGFR mutant resistant NSCLC.

13. Use of a TEAD inhibitor and a MEK inhibitor in the manufacture of a medicament for ~~A method of~~ treating cancer in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a TEAD inhibitor and a MEK inhibitor~~.

14. The ~~method~~use of claim 13, wherein the TEAD inhibitor is a compound of **Formula A**:



,

or a pharmaceutically acceptable salt thereof, wherein

L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

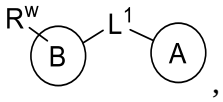
Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring

having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^W is an optionally substituted 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each R is independently -H or optionally substituted -C_{1-6} aliphatic. .

15. The ~~method~~use of claim 13, wherein the TEAD inhibitor is a compound of **Formula B**:



,

or a pharmaceutically acceptable salt thereof, wherein

L^1 is a covalent bond, or a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH($N(R)_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

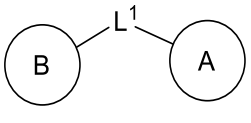
Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^w is a warhead group; wherein when R^w is a saturated or partially unsaturated monocyclic carbocyclic or heterocyclic ring, it optionally forms a spiro bicyclic ring with Ring B; and

each R is independently -H or optionally substituted -C_{1-6} aliphatic.

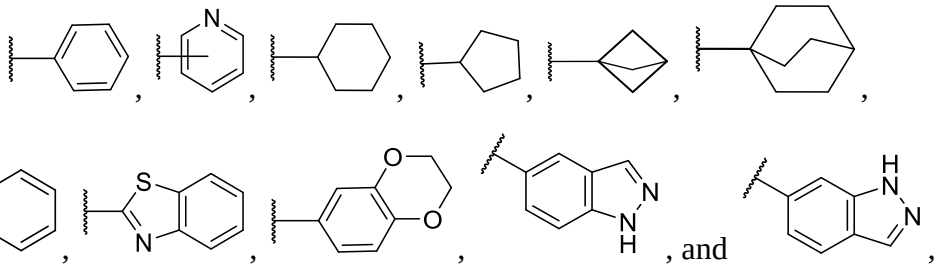
16. The ~~method~~use of claim 13, wherein the TEAD inhibitor is a compound of **Formula C**:



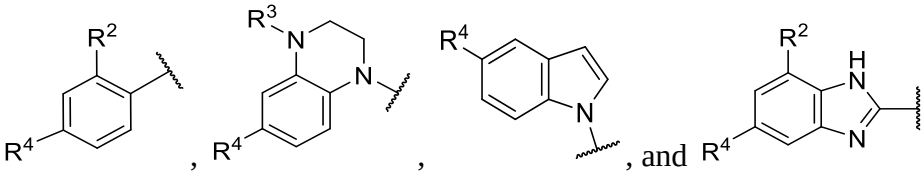
,

or a pharmaceutically acceptable salt thereof, wherein

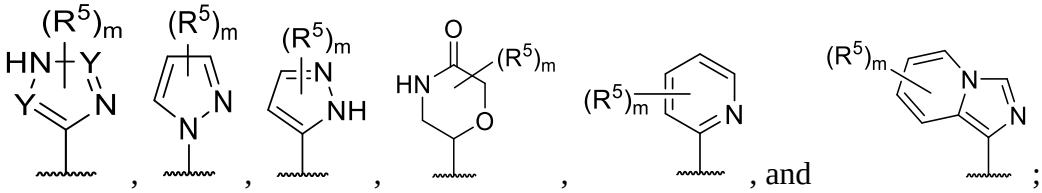
L^1 is a covalent bound, or a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

Ring A is selected from , and ,

each of which is optionally substituted;

Ring B is selected from ;

each R^2 is independently selected from -OR, -C(O)NR_2, optionally substituted -C_{1-6} aliphatic,

;

each Y is independently N or CR^5;

R^3 is H, -C(O)R, or optionally substituted -C_{1-6} aliphatic;

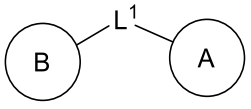
each R^4 is independently -$S(O)_2NR_2$, -$S(O)_2$R, -C(O)NR_2, -C(O)R, or optionally substituted -C_{1-6} aliphatic;

each R^5 is independently R, -CN, -C(O)R, -C(O)NR_2, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2; and

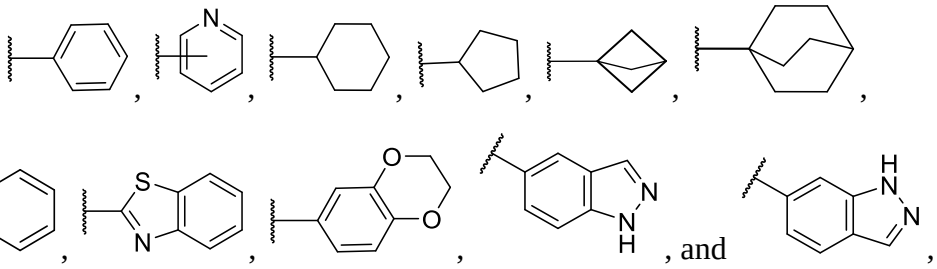
each R is independently H, optionally substituted -C_{1-6} aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

17. The ~~method~~use of claim 13, wherein the TEAD inhibitor is a compound of **Formula D**:

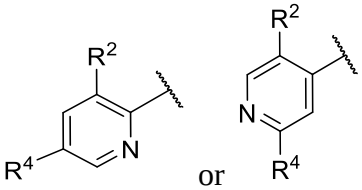


or a pharmaceutically acceptable salt thereof, wherein

L^1 is a covalent bound, or a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

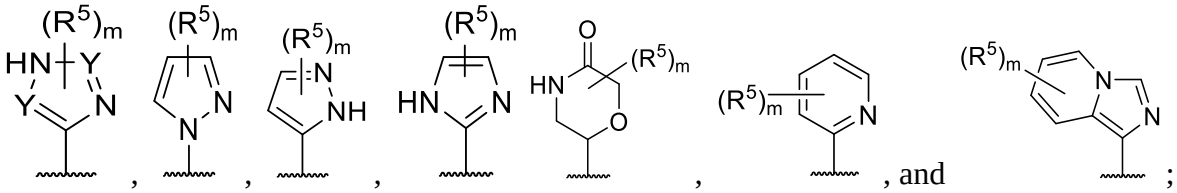
Ring A is selected from 

each of which is optionally substituted;

Ring B is 

;

each R^2 is independently selected from -OR, -C(O)NR_2, optionally substituted -C_{1-6} aliphatic,



;

each Y is independently N or CR^5;

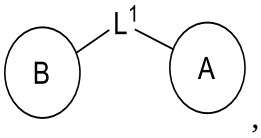
each R^4 is independently $-S(O)_2NR_2$, $-S(O)_2R$, $-C(O)NR_2$, $-C(O)R$, or optionally substituted $-C_{1-6}$ aliphatic;

each R^5 is independently R, -CN, $-C(O)R$, $-C(O)NR_2$, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2; and

each R is independently H, optionally substituted $-C_{1-6}$ aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

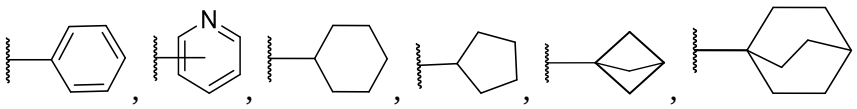
18. The ~~method~~use of claim 13, wherein the TEAD inhibitor is a compound of **Formula E**:

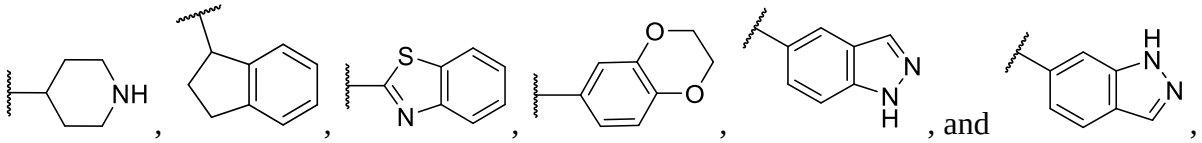


,

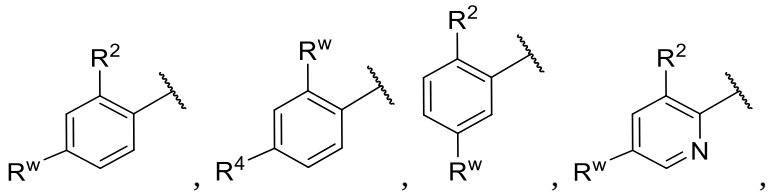
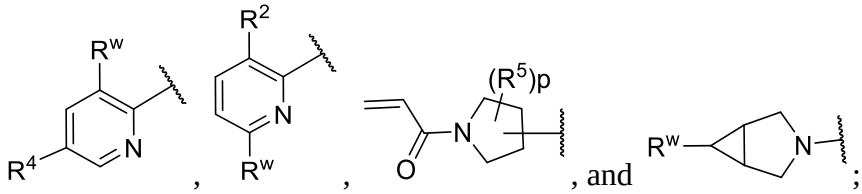
or a pharmaceutically acceptable salt thereof, wherein

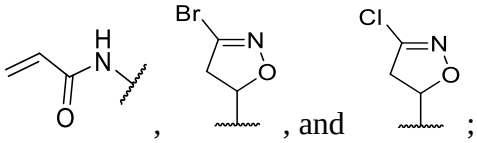
L^1 is a covalent bound, or a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

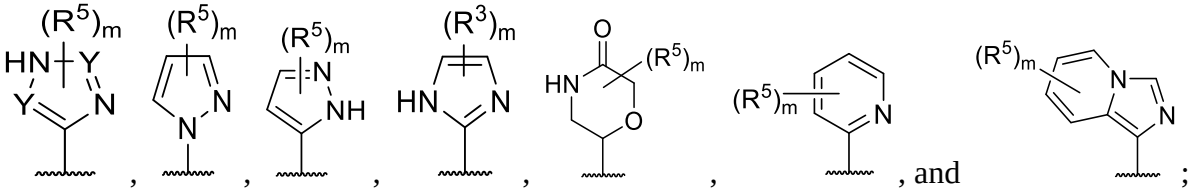
Ring A is selected from 

, 

, and , each of which is optionally substituted;

Ring B is selected from , , and ;

each R^w is independently selected from ;

each R^2 is independently selected from -OR, -C(O)NR_2, optionally substituted -C_{1-6} aliphatic, ;

each Y is independently N or CR^5;

each R^3 is independently H or optionally substituted -C_{1-6} aliphatic;

each R^4 is independently -$S(O)_2NR_2$, -$S(O)_2R$, -C(O)NR_2, -C(O)R, or optionally substituted -C_{1-6} aliphatic;

each R^5 is independently R, -CN, -C(O)R, -C(O)NR_2, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2;

p is 0, 1, or 2, and

each R is independently H, optionally substituted -C_{1-6} aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

19. The ~~method~~use of any one of claims 13-18, wherein the MEK inhibitor is selected from refametinib, selumetinib, trametinib, cobimetinib, binimetinib, mirdametinib, and pimasertib.

20. The ~~method~~use of any one of claims 13-19, wherein the cancer is a KRAS mutant cancer.

21. The ~~method~~use of claim 20, wherein the KRAS mutant cancer harbors one or more KRAS mutations selected from a KRAS G12C, a KRAS G12D mutation, a KRAS G12V mutation, and a KRAS G13 mutation.